THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH

2025 M Street, NW
Suite 800
Washington, DC 20036-3309, USA
Tel: (202) 367-1161
Fax: (202) 367-2161
E-mail: ASBMR@smithbucklin.com
Internet: www.asbmr.org

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir or Madam:

The American Society for Bone and Mineral Research is pleased to have the opportunity to respond to the request in the Federal Register for comments on clinical trial design in osteoporosis (Docket: 2004D-0035).

Is it appropriate to continue to use "placebo" controls in fracture-endpoint trials?
The ASBMR notes that true placebo controls are no longer used in fracture endpoint trials. All current studies use calcium and vitamin D, agents that are skeletally active. Placebo-controlled trials, while important for our understanding of drug efficacy, are currently limited in the U.S. by ethical, regulatory, and logistical considerations. For example, some investigators will not participate in fracture-endpoint trials for high risk patients due to ethical concerns; IRBs generally will not approve fracture-endpoint trials in high risk patients; and patient recruitment is often very difficult in such trials.

The ASBMR emphasizes the importance of informed consent in all clinical trials. Since some therapies are not available to all patients due to cost and accessibility, if patients understand and are willing to accept risk, participating in a clinical trial may give them a chance to obtain therapies which are otherwise unavailable to them.

The ASBMR recommends consideration of the following modifications of study design criteria for fracture-endpoint trials for FDA-required osteoporosis drug approval:

1. *Use of level of risk in inclusion criteria.*
   Patients *at high risk* for fracture should be excluded from placebo-controlled trials. Patients *at low* or *moderate risk* could be included.

   The ASBMR recognizes that there is no consensus on the definition of high risk, and that assessment of risk level may vary by institution, IRB, community and investigator. ASBMR considers patients with any prevalent hip fracture, multiple vertebral fracture, or recent fragility fracture including vertebral to be at high risk for fracture. It is not clear whether patients with a single recent vertebral fracture should be considered to be at high risk. Patients with low BMD (e.g., T-score of -3.0 or below) are at high risk. We suggest that absolute risk of hip and spine fracture is the preferred form of expressing fracture risk, and that the methodology for determining this should include BMD, age, prevalent fracture, and possibly other clinical risk factors. We support the efforts of the World Health Organization, under the direction of Dr. John

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Kanis, to develop an international standard for absolute fracture risk. ASBMR feels that an acceptable level of fracture risk in the "placebo" arm of a clinical trial is less than approximately 10-15% over three years.

2. *Studies of high risk patients.*
   ASBMR feels that high risk patients should still be studied in clinical trials, but that these patients would best be studied in either inferiority trials with known, effective FDA approved agents, or in trials that allow patients to take less robust antiresorptive drugs, such as calcitonin or raloxifene. The latter is being done with one current study: Novartis ZA2301.

Should fracture risk trials be 3 years in duration? Or could shorter studies provide adequate evidence of a new drug's effectiveness and safety?
A recent trial showed significant reduction in vertebral and nonvertebral fracture risk after median exposure of 19 months to an anabolic agent (Neer 2003). We feel that in high risk patients, a shorter exposure time than 3 years in a placebo-controlled trial is desirable in assessing efficacy in fracture risk reduction. However, there are concerns that a shorter time may not be sufficient to give a safety signal or proof of sustained affect. Long-term follow-up (e.g., 10 years without placebo control) is recommended to monitor safety and long-term benefit vs. risk.

Role of bone turnover markers.
Bone turnover markers should not be considered primary measures of treatment efficacy, and bone turnover markers alone are not surrogate markers for reduced fracture risk. Bone turnover markers are secondary endpoints which together with BMD, may assist in the evaluation of efficacy in prevention trials or help elucidate the mechanism of action of novel agents.

Role of other measures.
There is no single surrogate endpoint for fracture risk. Changes in BMD and bone turnover markers explains some but not all of the reduction in fracture rate in response to therapy. No current technology on the horizon seems better than these.

Sincerely,

On Behalf of the ASBMR Membership:

Robert A. Nissenson, Ph.D.
President

Joan R. Goldberg
Executive Director

Stuart L. Silverman, M.D.
Chair, Professional Practice Committee